II. Remarks

This Amendment is being submitted in response to the Final Office Action dated March 31, 2008. Applicants also respectfully request that the Examiner consider the references submitted with the enclosed Supplemental Information Disclosure Statement and the references previously submitted with the Supplemental Information Disclosure Statement submitted to the USPTO on March 28, 2008.

A. Status of the Claims

Claims 1-4, 6, 8, 14-17 and 21 are cancelled without prejudice or disclaimer of Applicants' right to pursue subject matter of those claims in one or more divisional applications. Claims 5, 7, 9-13, 18-20 and 22-47 are pending. Applicants have herein amended claims 5, 9, 12, 13, 18, 37 and 42.

Claim 5 has been amended to delete the term "general" as helpfully suggested by the Examiner. Also, claim 5 has been further amended to delete reference to "indol-2yl". Additionally, with regard to the proviso "R4 is a group represented by Formula II", claim 5 has also been amended to delete the reference to "R4 is a group represented by Formula II". These amendments are made for clarification purposes only and do not narrow the scope of the claim.

Support for the amendment to claim 5 can be found for example in the original specification, page 10, lines 8-9, and original claim 6 of the English translation of the specification as filed.

Claim 37 has been amended to delete the term "general" as helfully suggested by the Examiner. Claim 37 has also been amended such that the term "optionally substituted phenyl or monocyclic aromatic heterocycle" has been replaced with "a substituted or unsubstituted phenyl or monocyclic aromatic heterocycle". Claim 37 has also been amended to replace the term "can be the same or different and can be selected..." with

the term "independently selected.." These amendments are also made for clarification purposes only and do not narrow the scope of the claim.

The term "optionally substituted" has been deleted from amended claims 5, 12, 37 and 42 and replaced with the synonymous term "substituted or unsubstituted" for clarification and does not narrow the scope of these claims.

B. Rejection under 35 U.S.C. § 112, second paragraph

In the Office Action, the Examiner rejected claims 5 and 37 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner indicated that the term "general" with regard to Formula (V) is ambiguous... [and] should be deleted (See: Office Action, page 2, item 3, third paragraph). In response, the term "general" has been deleted from independent claims 5 and 37. This amendment is being made for clarification purposes only and does not narrow the scope of the claims.

The Examiner also indicated that the proviso "indol-2yl" is confusing. The Examiner stated that "the Ar^2 element in claims 5 and 37 have been defined to be optionally substituted phenyl or monocyclic aromatic heterocycle, this scope would not have encompassed any indolyl moiety" (See: Office Action, page 2, item 3, fourth paragraph). In response, the proviso "that indol-2yl is excluded" has been deleted from claims 5 and 37. This amendment is being made for clarification purposes and does not narrow the scope of the claim.

The Examiner further indicated that "in claim 5, the R^4 moiety has been limited to Formula II, therefore, the condition of R^4 being Formula II in the definition of Ar^2 what it cannot be is always enforced" (See: Office Action, page 2, item 3, paragraph 5). In response, the proviso "R^4 is a group represented by Formula II" has been deleted from

claim 5. This amendment is being made for clarification purposes and does not narrow the scope of the claim.

Finally, the Examiner indicated that "it is unclear whether claim 37 is within the scope of claim 5 or contains new matter because in claim 37, the phenyl or monocyclic aromatic heterocycles are optionally substituted without limitation while the Ar^2 when R^4 is formula II must be substituted with one or more groups selected from lower alkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl, and halogen" (See: Office Action page 2, item 3 last paragraph to page 3, first paragraph). The Examiner has requested that the scope of the claims be clearly defined with explicit antecedent basis pointed out from the specification.

In response, Applicants respectfully submit that claim 37 as amended differs in scope from amended claim 5 in that R^3 in claim 37 has been further limited to "a substituted or unsubstitued thienyl", whereas R^3 in claim 5 is "aryl or monocyclic aromatic heterocycle, each of which may be substituted". The Examiner is respectfully directed to the difference in claims 5 and 37. With respect to claim 5, it is only when R^3 is aryl or pyridyl that Ar^2 cannot be phenyl or pyridyl (See: claim 5). On the other hand, the proviso "that when R^3 is aryl or pyridyl... that Ar^2 cannot be phenyl or pyridyl...." is not recited in claim 37 as R^3 in claim 37 can only be a substituted or unsubstituted thienyl.

To address the Examiner's request that the scope of the claims be clearly defined with explicit antecedent basis pointed out from the specification, Applicant respectfully submits the following remarks, with enclosed Appendices Appendix A1-A5 for the Examiner's convenience:

Support for Formula (V) recited in independent claims 5 and 37 can be found for example in the English translation of the original specification at page 9, line 21 to page 10, line 1, and original claim 5 (See: Appendix A1).

Support for Ar^2 as recited in independent claims 5 and 7 ("Ar^2: a substituted or unsubstituted phenyl or monocyclic aromatic heterocycle") can be found for example in the English translation of the original specification at page 10, lines 8-9, and original claim 6 (See: Appendix A2).

Support for R^3 as recited in independent claim 5 ("R^3: aryl or monocyclic aromatic heterocycle, each of which may be substituted") can be found for example in the English translation of the original specification at page 10, line 5, referencing R^1 at page 6, lines 17-18, and original claim 5 (See: Appendix A3).

Support for R^3 as recited in independent claim 37 ("R^3: a substituted or unsubstituted thienyl") can be found for example in the English translation of the original specification at page 10, line 22 to page 11, line 1, and original claim 7 (See Appendix A4).

Support for R^4 as recited in independent claims 5 and 37 ("R^4: a group of Formula (II)") can be found for example in the English translation of the original specification at page 10, lines 6-7, referencing R^2 at page 6, line 19 to page 7, line 20, also at page 11, lines 7-11, and original claims 5 and 7 (See: Appendix A5).

In view of the amendments and support presented above, Applicant respectfully requests that the Examiner's § 112 rejections be withdrawn.

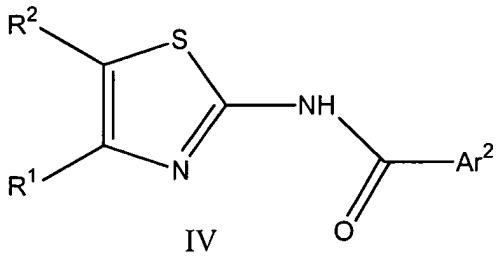
C. Rejection under 35 U.S.C. § 102(a) over Muto, et al.

In the Office Action, the Examiner rejected claims 5, 7, and 9-11 under 35 U.S.C. § 102(a) over Muto et al. CA 137 corresponding to published WO 02/049632. The Examiner indicated that "in the two translations of the priority documents, the Markush scope of the instant claims was not embraced since elements R^{20}, R^{21}, R^{22}, R^{23}, R^{26}, R^{27}, or R^{28}, are not found and the scope of these elements are not consistent with the

definition of the priority documents as R^{3-6}. Therefore, the benefit of priority date cannot be granted and the rejection is proper." (See: Office Action, page 3, item 3).

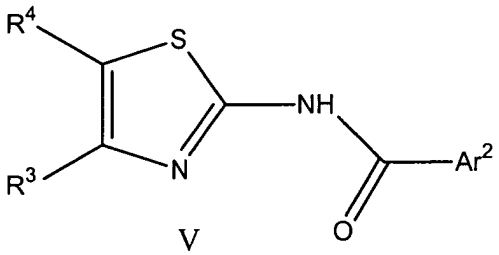
This rejection is respectfully traversed. With regard to the Examiner's assertion that "the Markush scope of the instant claims was not embraced since elements R^{20}, R^{21}, R^{22}, R^{23}, R^{26}, R^{27}, or R^{28}, are not found and the scope of these elements are not consistent with the definition of the priority documents as R^{3-6}", Applicants respectfully direct the Examiner's attention to the priority documents as follows:

JP priority documents 2002-10413 and JP 2002-10447 both disclose 2-acylaminothiazole derivatives represented by Formula IV (See: page 10, line 1 of JP 2002-10413 and page 9, line 17 of JP 2002-10447):



IV

Similarly, amended independent claims 5 and 37 (Formula V) of the present invention recite 2-acylaminothiazole derivative (See: page 10, line 1):



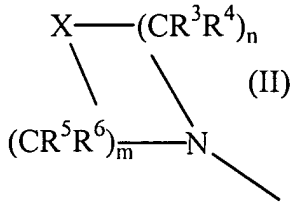
V

Both Formula IV as disclosed in both priority documents and Formula V recited in amended claims 5 and 37 of the present invention are identical with the exception that the

"R" substituents contained at the 4 and 5 positions of the thiazole ring are respectively labeled R^1 and R^2 in the priority documents (Formula IV) and R^3 and R^4 in the present application (Formula V). As can be seen from the illustration of Formula (IV) in both priority documents and Formula (V) of the present claims, R^2 and R^4 are both located at the 5 position of the thiazole ring. Accordingly, Applicant respectfully submits that the scope of the R^2 substituent corresponds to the scope of the R^4 substituent.

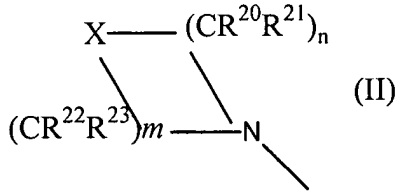
1. Scope of substituents R^{20}-R^{23}:

JP priority documents 2002-10413 and JP 2002-10447 both disclose R^2 represented by, *inter alia*, group (II):



(II)

Amended independent claims 5 and 37 recite, *inter alia*, R^4 represented by the formula (II):



(II)

Both Formula II disclosed in the priority documents and Formula II recited in amended claims 5 and 37 of the present invention are identical with the exception that the "R" substituents described by Formula II of the priority documents are labeled R^3, R^4, R^5 and R^6 and the "R" substituents described by Formula II as recited in amended claims 5 and

37 of the present invention are labeled R^{20}, R^{21}, R^{22} and R^{23}. Accordingly, Applicant respectfully submits that the scope of the R^3 and R^4 substituents described by the "$(CR^3R^4)_n$" group of Formula II disclosed in both JP priority documents correspond to the scope of the R^{20} and R^{21} substituents described by the "$(CR^{20}R^{21})_n$" group of Formula II recited in amended claims 5 and 37. In addition, Applicant respectfully submits that scope of the R^5 and R^6 substituents described by the "$(CR^5R^6)_m$" group of Formula II disclosed in both JP priority documents correspond to the scope of the R^{22} and R^{23} substituents described by the "$(CR^{22}R^{23})_m$" group of Formula II recited in amended claims 5 and 37.

In addition to the scope of substituents R^3-R^6 of Formula II disclosed in both JP priority documents corresponding to substituents R^{20}-R^{23} of Formula II recited in amended claims 5 and 37 of the present invention, Applicant respectfully submits that the scope of substituents R^{20}-R^{23} is also consistent with the scope of substituents R^3-R^6. To illustrate consistency of the scope of these substituents, Applicant directs the Examiner's attention to Table I in the enclosed Appendix B.

Applicants submit the following comparison of the R^3-R^6 Markush group in both priority documents with the corresponding R^{20}-R^{23} Markush group recited in amended claims 5 and 37:

The term "optionally substituted aralkyl" in the respective priority documents, page 8, lines 15-16 of JP App. 2002-10447 and page 9, lines 3-4 of JP App. 2002-10413, is synonymous with the term "optionally substituted arylalkyl" at page 7, lines 12-13 of the English translation of the specification as filed and as recited in amended claims 5 and 37.

The term "optionally substituted heteroarylalkyl" in the respective priority documents, page 8, lines 16-17 of JP App. 2002-10447 and page 9, lines 4-5 of JP App. 2002-10413, is synonymous with the term "optionally substituted aromatic heterocyclic

alkyl" at page 7, lines 13-14 of the English translation of the specification as filed and as recited in amended claims 5 and 37.

In view of the arguments presented above, it is respectfully submitted that the scope of substituents R^3-R^6 of Formula II disclosed in both JP priority documents and corresponding substituents R^{20}-R^{23} as claimed in amended claims 5 and 37 of the present invention are the same. Accordingly, Applicants respectfully request that the Examiner's 102(a) rejection be withdrawn.

2. Scope of substituents R^{26}-R^{28}:

Priority documents JP 2002-10413 and JP 2002-10447 disclose Formula (II), wherein X is a group represented by, *inter alia*, $N(R^9)$, or $C(R^{10})(R^{11})$. Similarly, amended independent claims 5 and 37 recite, *inter alia*, "X is a group represented by $N-(R^{26})$, or $C(R^{27})R^{28}$." Applicant respectfully submits that the scope of the groups "$N(R^9)$" and "$C(R^{10})(R^{11})$" disclosed in the priority documents in Formula II are identical to the scope of the groups "$N(R^{26})$" or "$C(R^{27})R^{28}$" recited in Formula II of amended claims 5 and 37.

In addition to the scope of substituents R^9-R^{11} of Formula II disclosed in both JP priority documents and substituents R^{26}-R^{28} of Formula II recited in amended claims 5 and 37 being identical, Applicant respectfully submits that the scope of substituents R^{26}-R^{28} is also consistent with the scope of substituents R^9-R^{11}. To illustrate consistency of the scope of these substituents, Applicant directs the Examiner's attention to Table II in the enclosed Appendix C.

Upon comparison of the R^9-R^{11} Markush group in both priority documents with the R^{26}-R^{28} Markush group recited in amended claims 5 and 37, the only differences are as follows:

The term "optionally substituted aralkyl" in the respective priority documents, page 8, lines 15-16 of JP App. 2002-10447 and page 9, lines 3-4 of JP App. 2002-10413, is synonymous with the term "optionally substituted arylalkyl" at page 7, lines 12-13 of the English translation of the specification as filed and as recited in amended claims 5 and 37.

The term "optionally substituted heteroarylalkyl" in the respective priority documents, page 8, lines 16-17 of JP App. 2002-10447 and page 9, lines 4-5 of JP App. 2002-10413, is synonymous with the term "optionally substituted aromatic heterocyclic alkyl" at page 7, lines 13-14 of the English translation of the specification as filed and as recited in amended claims 5 and 37.

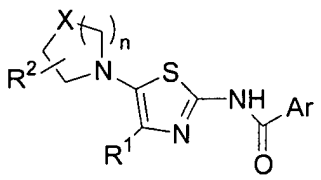
In view of the arguments presented above, it is respectfully submitted that the scope of substituents R^9-R^{11} of Formula II disclosed in both JP priority documents and substituents R^{26}-R^{28} as claimed in amended claims 5 and 37 of the present invention are the same. Accordingly, Accordingly, Applicants respectfully request that the Examiner's 102(a) rejection be withdrawn.

D. Rejection under 35 U.S.C. § 102(e), (f) or (g) over U.S. 2004/0077697

In the Office Action, the Examiner rejected claims 5, 7, 9-13, and 18-47 under 35 U.S.C. §102(e), (f) and (g) over U.S. 2004/0077697. The Examiner indicated that the '697 publication has a filing date prior to the filing date of the instant application. The Examiner also indicated that "abandoning a claim to the same invention... will resolve the issues under 35 U.S.C. § 102(e) and (g)..., but it does not resolve the 102(f) issue." The Examiner further asserted that "the assignee is required to make it of record by stating which entity is the first inventor of the subject matter upon presentation of such evidence." (See: Office Action, page 3, item 4).

It is respectfully submitted that the indicated overlap between the present claims and the structures described in the '697 publication is a misunderstanding. As originally filed, and as currently presented, the proviso in claim 5 specifically excluded the possibility of overlap with the '697 publication. In particular, the proviso excluded verbatim the definition of R^1 in the '697 publication (which corresponds to the 4-position on the thiazole ring, as R^3 in Applicant's case). Therefore, none of Applicant's compounds are described in the '697 publication.

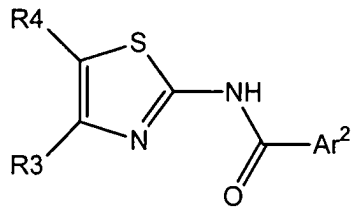
The '697 publication discloses compounds of Formula I:



wherein Ar represents phenyl or pyridyl each of which can be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl, and halogen (See: page 2, paragraph [0018] of the '697 publication, attached hereto as Appendix D).

The '697 publication also discloses R^1 represents aryl or pyridyl, each of which can be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl, and halogen (See: page 2, paragraph [0019] of the '697 publication, attached hereto as Appendix D).

Claim 5 of the present invention recites, in pertinent part, a 2-acylaminothiazole derivative represented by Formula V or a pharmaceutically acceptable salt thereof:



(V)

Similar to the Ar substituent disclosed in the '697 publication, Ar^2 in present independent claim 5 can also encompass a phenyl or pyridyl group. However, in contrast to the disclosure of the '697 publication, the proviso recited in independent claim 5 of the present invention does not permit Ar^2 to be phenyl or pyridyl when R^3 is aryl or pyridyl, each of which can be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl, and halogen. Accordingly, the structures encompassed by independent claim 5 of the present invention are not described by Formula I of the '697 publication.

In view of the above, Applicants respectfully submit that there is no overlap of subject matter between Applicant's case and the '697 publication, therefore, the structures described in the claims of the present invention cannot be the same as the structures disclosed in the'697 publication. Accordingly, there should be no remaining issue under 35 U.S.C. §102(e), §102 (f) or §102(g) referenced against Applicant. Therefore, Applicants respectfully submit that the Examiner's rejection be withdrawn.

III. CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims. A check in the amount of $180.00 is enclosed herewith for the fee due for submission of the enclosed Supplemental Information Disclosure Statement. It is believed that no additional fees are due for this submission. However, if it is determined that any fees are due or that any fee has been overpaid, the Commissioner for Patents is hereby authorized to charge said fees or credit any overpayments to Deposit Account No. 50-0552.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

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Appendix B

Table I

Application No.	Page/line	Substituent	Scope
JP Priority App. No. 2002-10413	Page 9, lines 1-11	R^3-R^6	which may be identical or different, –H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted aralkyl; optionally substituted aromatic heterocycle; optionally substituted heteroarylalkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl, or -O-aryl, and cycloalkyl; -NHCO-lower alkyl; and oxo.
JP Priority App. No. 2002-10447	Page 8, line 13, to page 9, line3	R^3-R^6	which may be identical or different, –H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted aralkyl; optionally substituted aromatic heterocycle; optionally substituted heteroarylalkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl, or -O-aryl, and cycloalkyl; -NHCO-lower alkyl; and oxo.
U.S. 10/500,964	Amended claims 5 and 37	R^{20}-R^{23}	is independently selected from the group consisting of –H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted arylalkyl; optionally substituted aromatic heterocycle; optionally substituted aromatic heterocyclic alkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl, or -O-aryl, and cycloalkyl; -NHCO-lower alkyl; and oxo.

Appendix C

Table II

Application No.	Page/line	Substituent	Scope
JP Priority App. No. 2002-10413	Page 9, lines 1-11	R^9-R^{11}	which may be identical or different, –H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted aralkyl; optionally substituted aromatic heterocycle; optionally substituted heteroarylalkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl, or -O-aryl, and cycloalkyl; -NHCO-lower alkyl; and oxo.
JP Priority App. No. 2002-10447	Page 8, line 13, to page 9, line3	R^9-R^{11}	which may be identical or different, –H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted aralkyl; optionally substituted aromatic heterocycle; optionally substituted heteroarylalkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl, or -O-aryl, and cycloalkyl; -NHCO-lower alkyl; and oxo.
U.S. 10/500,964	Amended claims 5 and 37	R^{26}-R^{28}	is independently selected from the group consisting of –H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted arylalkyl; optionally substituted aromatic heterocycle; optionally substituted aromatic heterocyclic alkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl, or -O-aryl, and cycloalkyl; -NHCO-lower alkyl; and oxo.

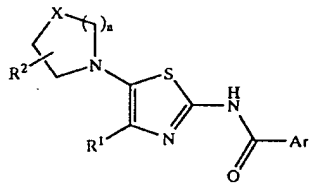
Appendix D

platelet increasing activity. As a result, it has been found that a novel 2-acylaminothiazole derivative has a superior platelet increasing activity, leading to accomplishment of the invention.

[0015] The compound of the invention is a 2-acylaminothiazole derivative structurally characterized in that an acylamino group is substituted at the 2-position thereof and that a nitrogen atom of a nitrogen-containing heterocycle is directly bound to the 5-position thereof. Further, the compound of the invention is pharmacologically characterized by having a platelet increasing activity based on a megakaryocyte colony formation promoting action.

[0016] Specifically, according to the invention, there is provided a 2-acylaminothiazole derivative represented by the following general formula (I) or a pharmaceutically acceptable salt thereof, which is useful as a therapeutic agent for thrombocytopenia.

(I)



[0017] In the formula, the symbols have the following meanings:

[0018] Ar represents phenyl or pyridyl, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl, —CO-lower alkyl, —COO-lower alkyl, —OH, —O-lower alkyl, —OCO-lower alkyl, and halogen;

[0019] R^1 represents aryl or pyridyl, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl, —CO-lower alkyl, —COO-lower alkyl, —OH, —O-lower alkyl, —OCO-lower alkyl, and halogen;

[0020] R^2 represents a group selected from the group consisting of —H, —OH, —COOH, —COO-lower alkyl, carbamoyl which may be substituted with one or two lower alkyls, amino which may be substituted with one or two lower alkyls, and cyclic amino, provided that one or more of this group may be present on the ring;

[0021] —X— represents —CH_2—, —O—, —S—, or —$N(R^3)$—;

[0022] R^3 represents optionally substituted lower alkyl, cycloalkyl, optionally substituted aryl, optionally substituted aryl-lower alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl-lower alkyl, —CO-lower alkyl, —COO-lower alkyl, or carbamoyl which may be substituted one or two lower alkyls; and

[0023] n represents an integer of from 1 to 3.

[0024] Compounds represented by the foregoing general formula (I), wherein X represents —$N(R^3)$—, and n is 2 or 3, or pharmaceutically acceptable salts thereof are preferable. Compounds represented by the foregoing general formula (I), wherein X represents —$N(R^3)$—, n is 2 or 3, and Ar represents phenyl or pyridyl, each of which may be substituted with one or more groups selected from the group consisting of —OH, —O-lower alkyl, and —OCO-lower alkyl, or pharmaceutically acceptable salts thereof are more preferable. Particularly preferred examples include:

[0025] 3,5-dimethoxy-N-(5-morpholin-4-yl-4-phenylthiazol-2-yl)benzamide, N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-2-methoxyisonicotinamide,

[0026] 3-chloro-N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-hydroxybenzamide,

[0027] 3,5-dimethoxy-N-(5-piperidin-1-yl-4-pyridin-4-ylthiazol-2-yl)benzam ide, or

[0028] 4-{[5-(4-cyclohexylpiperazin-1-yl)-4-phenylthiazol-2-yl]carbamoyl}ph enyl acetate, or

[0029] pharmaceutically acceptable salts thereof.

[0030] Further, according to the invention, there is provided a pharmaceutical composition comprising, as an active ingredient, a compound represented by the foregoing general formula (I); a compound represented by the foregoing general formula (I), wherein X represents —$N(R^3)$—, and n is 2 or 3; a compound represented by the foregoing general formula (I), wherein X represents —$N(R^3)$—, n is 2 or 3, and Ar represents phenyl or pyridyl, each of which may be substituted with one or more groups selected from the group consisting of —OH, —O-lower alkyl, and —OCO-lower alkyl; or a pharmaceutically acceptable salt thereof. Concretely, the foregoing pharmaceutical composition is a pharmaceutical composition as a megakaryocyte colony forming promoter, a pharmaceutical composition as a platelet increasing agent, or a pharmaceutical composition as a therapeutic agent for thrombocytopenia.

[0031] The compounds of the invention will be further described below.

[0032] In this description, the term "lower alkyl" means a linear or branched carbon chain having from 1 to 6 carbon atoms (C_{1-6}), and specific examples include methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, neopentyl, and hexyl, etc. Of these are preferable C_{1-3} alkyls including methyl, ethyl, propyl and isopropyl. Examples of the substituent acceptable in the "optionally substituted lower alkyl" for R^3 include —O-lower alkyl and —O-aryl, etc.

[0033] The term "aryl" means an aromatic ring comprising carbon atoms and is preferably a monocyclic to tricyclic aromatic ring having from 6 to 14 carbon atoms (C_{6-14}). Specific examples include phenyl and naphthyl, with phenyl being preferred. Examples of the substituent acceptable in the "optionally substituted aryl" and "optionally substituted aryl-lower alkyl" for R^3 include lower alkyl, —O-lower alkyl, halogen, nitro, and cyano, etc.

[0034] The term "heteroaryl" means a monovalent group of a monocyclic to tricyclic aromatic ring having one or more hetero atom such as nitrogen, oxygen, and sulfur, and specific examples include pyridyl, pyrazyl, pyridazyl, pyrrolyl, imidazolyl, thienyl, furanyl, thiazolyl, oxazolyl, indolyl, quinolyl, and benzothiazolyl, etc. Examples of the

phenyl or thienyl, each of which is substituted with 1 to 3 halogen atoms (when substituted with 2 or 3 halogen atoms, the halogen atoms may be identical or different.).

R^2 in the compound of the general Formula (I) is preferably a group represented by the general Formula (II); more preferably, a group represented by the general Formula (II) wherein n is 2, m is 2, and X is a group represented by N-R^{26} or C(-R^{27})-R^{28}; still more preferably, 4-(piperidin-1-yl)piperidin-1-yl, 4-propylpiperidin-1-yl, 4-cyclohexylpiperazin-1-yl, or 4-propylpiperazin-1-yl.

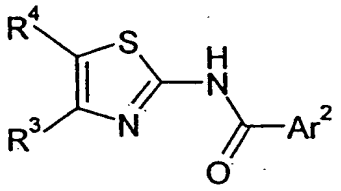
(2) The pharmaceutical composition according to (1) wherein R^1 is phenyl or thienyl, each of which may be substituted with 1 to 3 halogen atoms (when substituted with 2 or 3 halogen atoms, the halogen atoms may be identical or different); R^2 is a group represented by the general Formula (II), (wherein n is 2, m is 2, and X is a group represented by N-R^{26} or C(-R^{27})-R^{28}); and Ar^1 is phenyl or pyridyl, each of which may be substituted.

(3) The pharmaceutical composition according to (1) or (2), wherein the pharmaceutical composition is used as a therapeutic agent for thrombocytopenia.

(4) The pharmaceutical composition according to (1) or (2), wherein the pharmaceutical composition is used as a c-Mpl ligand.

(5) A 2-acylaminothiazole derivative represented by the following general Formula (V) or a pharmaceutically acceptable salt thereof:

Appendix A, cont'd



(V)

wherein symbols have the following meaning,

Ar^2: a group represented by Ar^1 as described in (1), with the proviso that indol-2-yl is excluded,

R^3: a group represented by R^1 as described in (1),

R^4: a group represented by R^2 as described in (1), with the proviso that a group represented by the general Formula (IV) is excluded.

Ar^2 in the compound of the general Formula (V) is preferably phenyl or monocyclic aromatic heterocycle, each of which may be substituted;

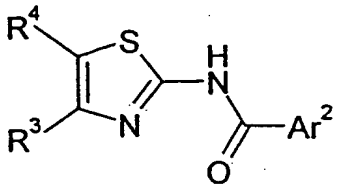
more preferably, phenyl or pyridyl, each of which may be substituted;

still more preferably, phenyl which is unsubstituted at 2- and 6-positions, substituted with -H, -F, -Cl, or -Br at 3-position, substituted with -F, -Cl, or -Br at 5-position, and substituted at 4-position, or pyridin-3-yl which is unsubstituted at 2- and 4-positions, substituted with -F, -Cl, or -Br at 5-position, and substituted at 6- position;

most preferably, phenyl substituted at 4-position with a substituent group selected from the group consisting of $-O-R^Y$, $-NH-R^Y$, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl, or pyridin-3-yl which is substituted at 6-position with a substituent group selected from the group consisting of $-O-R^Y$, $-NH-R^Y$, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl.

R^3 in the compound of the general Formula (V) is preferably phenyl or

Appendix A_2



(V)

wherein symbols have the following meaning,

Ar^2: a group represented by Ar^1 as described in (1), with the proviso that indol-2-yl is excluded,

R^3: a group represented by R^1 as described in (1),

R^4: a group represented by R^2 as described in (1), with the proviso that a group represented by the general Formula (IV) is excluded.

Ar^2 in the compound of the general Formula (V) is preferably phenyl or monocyclic aromatic heterocycle, each of which may be substituted;

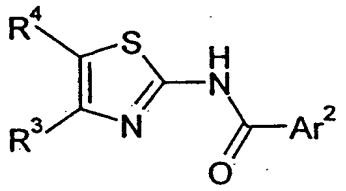
more preferably, phenyl or pyridyl, each of which may be substituted;

still more preferably, phenyl which is unsubstituted at 2- and 6-positions, substituted with -H, -F, -Cl, or -Br at 3-position, substituted with -F, -Cl, or -Br at 5-position, and substituted at 4-position, or pyridin-3-yl which is unsubstituted at 2- and 4-positions, substituted with -F, -Cl, or -Br at 5-position, and substituted at 6- position;

most preferably, phenyl substituted at 4-position with a substituent group selected from the group consisting of -O-R^Y, -NH-R^Y, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl, or pyridin-3-yl which is substituted at 6-position with a substituent group selected from the group consisting of -O-R^Y, -NH-R^Y, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl.

R^3 in the compound of the general Formula (V) is preferably phenyl or

Appendix A3



(V)

wherein symbols have the following meaning,

Ar^2: a group represented by Ar^1 as described in (1), with the proviso that indol-2-yl is excluded,

R^3: a group represented by R^1 as described in (1),

R^4: a group represented by R^2 as described in (1), with the proviso that a group represented by the general Formula (IV) is excluded.

Ar^2 in the compound of the general Formula (V) is preferably phenyl or monocyclic aromatic heterocycle, each of which may be substituted;

more preferably, phenyl or pyridyl, each of which may be substituted;

still more preferably, phenyl which is unsubstituted at 2- and 6-positions, substituted with -H, -F, -Cl, or -Br at 3-position, substituted with -F, -Cl, or -Br at 5-position, and substituted at 4-position, or pyridin-3-yl which is unsubstituted at 2- and 4-positions, substituted with -F, -Cl, or -Br at 5-position, and substituted at 6- position;

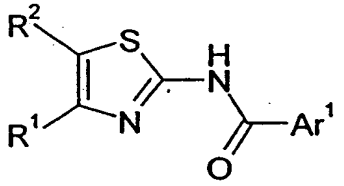
most preferably, phenyl substituted at 4-position with a substituent group selected from the group consisting of $-O-R^Y$, $-NH-R^Y$, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl, or pyridin-3-yl which is substituted at 6-position with a substituent group selected from the group consisting of $-O-R^Y$, $-NH-R^Y$, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl.

R^3 in the compound of the general Formula (V) is preferably phenyl or

Appendix A_3
cont'd

The present invention relates to the following aspects (1)~(17).

(1) A pharmaceutical composition for increasing the number of platelets comprising a 2-acylaminothiazole derivative represented by the following general Formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient:



(I)

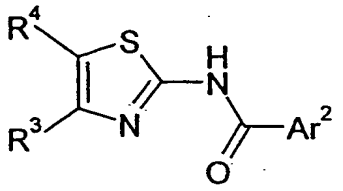
wherein symbols have the following meanings:

Ar^1: aryl, monocyclic aromatic heterocycle, or bicyclic condensed heterocycle, each of which may be substituted (with the proviso that when R^1 is aryl or pyridyl, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl, and halogen atom, and R^2 is a group represented by the following general Formula (II); Ar^1 is not phenyl or pyridyl, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl, and halogen atom.),

R^1: aryl or monocyclic aromatic heterocycle, each of which may be substituted,

R^2: a group represented by the following general Formula (II), (III) or (IV):

Appendix A4



(V)

wherein symbols have the following meaning,

Ar^2: a group represented by Ar^1 as described in (1), with the proviso that indol-2-yl is excluded,

R^3: a group represented by R^1 as described in (1),

R^4: a group represented by R^2 as described in (1), with the proviso that a group represented by the general Formula (IV) is excluded.

Ar^2 in the compound of the general Formula (V) is preferably phenyl or monocyclic aromatic heterocycle, each of which may be substituted;

more preferably, phenyl or pyridyl, each of which may be substituted;

still more preferably, phenyl which is unsubstituted at 2- and 6-positions, substituted with -H, -F, -Cl, or -Br at 3-position, substituted with -F, -Cl, or -Br at 5-position, and substituted at 4-position, or pyridin-3-yl which is unsubstituted at 2- and 4-positions, substituted with -F, -Cl, or -Br at 5-position, and substituted at 6- position;

most preferably, phenyl substituted at 4-position with a substituent group selected from the group consisting of -O-R^Y, -NH-R^Y, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl, or pyridin-3-yl which is substituted at 6-position with a substituent group selected from the group consisting of -O-R^Y, -NH-R^Y, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl.

→ R^3 in the compound of the general Formula (V) is preferably phenyl or

Appendix A4
cont'd

thienyl, each of which may be substituted; more preferably, phenyl or thienyl, each of which may be substituted with one or more groups selected from the group consisting of halogen atom and trifluoromethyl; still more preferably, phenyl or thienyl, each of which is substituted with 1 to 3 halogen atoms (when substituted with 2 or 3 halogen atoms, the halogen atom may be identical or different.)

R^4 in the compound of the general Formula (V) is preferably a group represented by the general Formula (II), more preferably a group represented by the general Formula (II) wherein n is 2, m is 2, and X is N-R^{26} or C-(R^{27})-R^{28}; still more preferably, 4-(piperidin-1-yl)piperidin-1-yl, 4-propylpiperidin-1-yl, 4-cyclohexylpiperazin-1-yl, or 4-propylpiperazin-1-yl.

(6) The compound according to (5), wherein Ar^2 is phenyl or monocyclic aromatic heterocycle, each of which may be substituted.

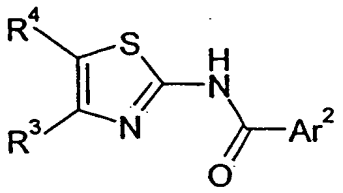
(7) The compound according to (6), wherein R^3 is phenyl or thienyl, each or which may be substituted; R^4 is a group represented by the general Formula (II); Ar^2 is phenyl or pyridyl, each of which may be substituted.

(8) The compound according to (7), wherein n is 2, m is 2, and X is a group represented by N-R^{26} or C(-R^{27})-R^{28}.

(9) The compound according to (8), wherein R^3 is phenyl or thienyl, each of which is substituted with 1 to 3 halogen atoms (when substituted with 2 or 3 halogen atoms, the halogen atoms may be identical or different.).

(10) The compound according to (9), wherein R^4 is 4-(piperidin-1-yl)piperidin-1-yl, 4-propylpiperidin-1-yl, 4-cyclohexylpiperazin-1-yl, or 4-propylpiperazin-1-yl.

Appendix A5



(V)

wherein symbols have the following meaning,

Ar^2: a group represented by Ar^1 as described in (1), with the proviso that indol-2-yl is excluded,

R^3: a group represented by R^1 as described in (1),

R^4: a group represented by R^2 as described in (1), with the proviso that a group represented by the general Formula (IV) is excluded.

Ar^2 in the compound of the general Formula (V) is preferably phenyl or monocyclic aromatic heterocycle, each of which may be substituted;

more preferably, phenyl or pyridyl, each of which may be substituted;

still more preferably, phenyl which is unsubstituted at 2- and 6-positions, substituted with -H, -F, -Cl, or -Br at 3-position, substituted with -F, -Cl, or -Br at 5-position, and substituted at 4-position, or pyridin-3-yl which is unsubstituted at 2- and 4-positions, substituted with -F, -Cl, or -Br at 5-position, and substituted at 6- position;

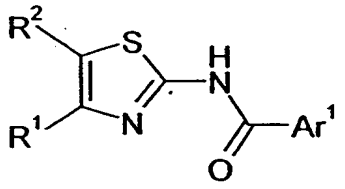
most preferably, phenyl substituted at 4-position with a substituent group selected from the group consisting of $-O-R^Y$, $-NH-R^Y$, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl, or pyridin-3-yl which is substituted at 6-position with a substituent group selected from the group consisting of $-O-R^Y$, $-NH-R^Y$, optionally substituted piperidin-1-yl and optionally substituted piperazin-1-yl.

R^3 in the compound of the general Formula (V) is preferably phenyl or

Appendix A5
cont'd

The present invention relates to the following aspects (1)~(17).

(1) A pharmaceutical composition for increasing the number of platelets comprising a 2-acylaminothiazole derivative represented by the following general Formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient:



(I)

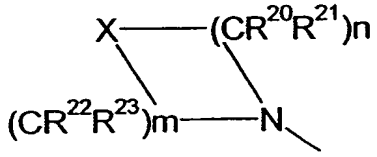
wherein symbols have the following meanings:

Ar^1: aryl, monocyclic aromatic heterocycle, or bicyclic condensed heterocycle, each of which may be substituted (with the proviso that when R^1 is aryl or pyridyl, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl, and halogen atom, and R^2 is a group represented by the following general Formula (II); Ar^1 is not phenyl or pyridyl, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl, and halogen atom.),

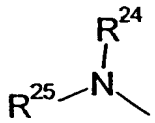
R^1: aryl or monocyclic aromatic heterocycle, each of which may be substituted,

R^2: a group represented by the following general Formula (II), (III) or (IV):

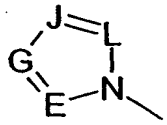
Appendix A5
cont'd



(II)



(III)



(IV)

wherein symbols have the following meanings:

n: an integer of 1 to 3,

m: an integer of 1 to 3,

(when n or m is an integer of 2 or more, $CR^{20}R^{21}$ and $CR^{22}R^{23}$ may be identical or different.)

X: O, S, or a group represented by $N\text{-}R^{26}$ or $C(\text{-}R^{27})\text{-}R^{28}$,

E, G, J, L: independently N or a group represented by $C\text{-}R^{29}$, with the proviso that at least one of them is $C\text{-}R^{29}$,

R^{20}, R^{21}, R^{22}, R^{23}, R^{26}, R^{27}, R^{28}, R^{29}: which may be identical or different -H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted arylalkyl; optionally substituted aromatic heterocycle; optionally substituted aromatic heterocyclic alkyl; optionally substituted nonaromatic heterocycle; optionally substituted lower alkenyl; optionally substituted lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl and cycloalkyl, each of which may be substituted with halogen, -OH, -O-lower alkyl, or -O-aryl; -NHCO-lower alkyl; or oxo.

R^{24}, R^{25}: which may be identical or different, -H, optionally substituted lower alkyl, optionally substituted cycloalkyl, or optionally substituted

thienyl, each of which may be substituted; more preferably, phenyl or thienyl, each of which may be substituted with one or more groups selected from the group consisting of halogen atom and trifluoromethyl; still more preferably, phenyl or thienyl, each of which is substituted with 1 to 3 halogen atoms (when substituted with 2 or 3 halogen atoms, the halogen atom may be identical or different.)

R^4 in the compound of the general Formula (V) is preferably a group represented by the general Formula (II), more preferably a group represented by the general Formula (II) wherein n is 2, m is 2, and X is N-R^{26} or C-(R^{27})-R^{28}; still more preferably, 4-(piperidin-1-yl)piperidin-1-yl, 4-propylpiperidin-1-yl, 4-cyclohexylpiperazin-1-yl, or 4-propylpiperazin-1-yl.

(6) The compound according to (5), wherein Ar^2 is phenyl or monocyclic aromatic heterocycle, each of which may be substituted.

(7) The compound according to (6), wherein R^3 is phenyl or thienyl, each or which may be substituted; R^4 is a group represented by the general Formula (II); Ar^2 is phenyl or pyridyl, each of which may be substituted.

(8) The compound according to (7), wherein n is 2, m is 2, and X is a group represented by N-R^{26} or C(-R^{27})-R^{28}.

(9) The compound according to (8), wherein R^3 is phenyl or thienyl, each of which is substituted with 1 to 3 halogen atoms (when substituted with 2 or 3 halogen atoms, the halogen atoms may be identical or different.).

(10) The compound according to (9), wherein R^4 is 4-(piperidin-1-yl)piperidin-1-yl, 4-propylpiperidin-1-yl, 4-cyclohexylpiperazin-1-yl, or 4-propylpiperazin-1-yl.

Appendix E

Office Action Summary	Application No.	Applicant(s)	
	11/593,758	SUZUKI ET AL.	
	Examiner	Art Unit	
	Joseph S. Kudla	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 37* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Election/Restrictions

1. Applicant's January 22, 2008 correspondence elects Group I, without traverse, which encompasses claims 1-10 and 37. Claims 11-36 have been cancelled which represented inventions II-VI. Applicant's correspondence elected 1-[3-chloro-5-[[[4-(4-chloro-2-thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl]amino]carbonyl]-2-pyridinyl]- 4-Piperidinecarboxylic acid as the compound. Accordingly, the subject matter now under consideration is drawn to claims 1-10 and 37.

Priority

2. This application claims priority to U.S. Provisional Patent Application 60/734426, filed November 8, 2005. Priority is acknowledged.

Information Disclosure Statement

3. The Information Disclosure Statement (IDS) correspondence submitted by Applicant on August 06, 2007 is acknowledged and has been reviewed.

Claim Objections

4. Claim 10 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim 10 not been further treated on the merits.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

a. The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

b. The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The language "therapeutically effective amount" in claim 1 is indefinite. The Examiner is unable to ascertain from the instant specification what the term "therapeutically effective amount" encompasses. Without further disclosure from Applicant, the phrase is unclear and confusing.

6. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention.

The dual use of the language "mg/day" and "mg/kg/day" in claim 37 is indefinite. The Examiner is unable to ascertain from the instant specification which term applicant meant, as both are used throughout the instant specification. Without further disclosure from Applicant, the phrase is unclear and confusing. The Examiner will assume at this time in the prosecution of the case that the value is "mg/kg/day".

Appropriate action is required.

7. Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Applicant claims "polymorph" and "derivative" in instant claims 4 and 5. Because the instant specification does not provide written description of what structures are contemplated for such "polymorphs" and "derivatives," the phrases lack adequate written description.

Regarding the requirement for adequate written description of chemical entities, Applicants' attention is directed to MPEP § 2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F. 3d 1559, 1568 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an

adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish list or plan for obtaining the claimed chemical invention." Eli Lilly, 119 F. 3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem Inc. v. Gen-Probe Inc.*, 296 F. 3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. At 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant has failed to provide any written description for "polymorphs" and "derivatives" in the instant specification. As such, it is not apparent that Applicant was actually in possession of, and intended to use, within the context of the present invention, any polymorphs or derivatives of any of the compounds found within the instant specification, at the time the present invention was made.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claim 37 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sugasawa et al. (International Application WO 03/062233 and cited by Applicant) The English language equivalent of the National Stage entry of WO 03/062233 document is U.S. Patent Publication US 2005/0153977. All citations will be made from the English language equivalent.

Sugasawa et al. teach compounds with a 2-acylaminothiazole core (page 2, paragraph 29) that are effective in increasing platelet formation activity (page 2, paragraph 27). Sugasawa et al. teach pharmaceutical compositions of the 2-acylaminothiazole core compounds (page 11, paragraphs 222-225) and that compounds with this core are administered in a daily dose range of 0.0001 to 50 mg/mL (page 11 and 12, paragraph 226). Sugasawa et al. teach that one of the specific compounds that are effective includes 1-[3-chloro-5-[[[4-(4-chloro-2-

thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl]amino]carbonyl]-2-pyridinyl]- 4-Piperidinecarboxylic acid (page 46, table 24, compound A0427).

9. Claim 37 is rejected under 35 U.S.C. 102(e) as being anticipated by Sugasawa et al. (U.S. Patent Publication US 2005/0153977).

The applied reference has common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Sugasawa et al. teach compounds with a 2-acylaminothiazole core (page 2, paragraph 29) that are effective in increasing platelet formation activity (page 2, paragraph 27). Sugasawa et al. teach pharmaceutical compositions of the 2-acylaminothiazole core compounds (page 11, paragraphs 222-225) and that compounds with this core are administered in a daily dose range of 0.0001 to 50 mg/mL (page 11 and 12, paragraph 226). Sugasawa et al. teach that one of the specific compounds that are effective includes 1-[3-chloro-5-[[[4-(4-chloro-2-thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl]amino]carbonyl]-2-pyridinyl]- 4-Piperidinecarboxylic acid (page 46, table 24, compound A0427).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Sugasawa et al. (International Application WO 03/062233 and cited by Applicant) (The English language equivalent of the National Stage entry of WO 03/062233 document is U.S. Patent Publication US 2005/0153977. All citations will be made from the English language equivalent.), in view of all Vadhan-Raj et al. ("Recombinant Human Thrombopoietin Attenuates Carboplatin-Induced Severe Thrombocytopenia and the Need for Platelet Transfusions in Patients with Gynecologic Cancer," 2000, Annuals of Internal Medicine, Volume 132, Number 5, Pages 364-8 and cited by Applicant) and Mutschler et al. (Drug Actions: Basic Principles and Therapeutic Aspects, 1995, CRC Press, pages 6-8).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that

the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Sugasawa et al. teach compounds with a 2-acylaminothiazole core (page 2, paragraph 29) that are effective in increasing platelet formation activity (page 2, paragraph 27). Sugasawa et al. teach pharmaceutical compositions of the 2-acylaminothiazole core compounds (page 11, paragraphs 222-225) and that compounds with this core are administered in a daily dose range of 0.0001 to 50 mg/mL (page 11 and 12, paragraph 226). Sugasawa et al. teach that one of the specific compounds that are effective includes 1-[3-chloro-5-[[[4-(4-chloro-2-thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl]amino]carbonyl]-2-pyridinyl]- 4-Piperidinecarboxylic acid (page 46, table 24, compound A0427). Sugasawa et al. teach pharmaceutically acceptable excipients and that the dosage form could range from tablets to capsules to parental delivery (page 11 and paragraphs 223-5).

Sugasawa et al. do not teach the use of rhTPO or immediate or controlled release dosage characteristics.

Vadhan-Raj et al. teach that rhTPO is effective at increasing platlet counts in a human cancer subject (page 364, column 1, within Results, first sentence).

Mutschler et al. teach drug administration depends on the site, route and the dosage form and dosage form is dependent on the physical and chemical properties, the desired onset of activity and duration of effect, the desired site of action for the drug and the condition of the patient (page 6, under Drug Administration, first paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention in view of the teachings of Sugasawa et al. and Vadhan-Raj et al. which both disclose compounds useful in increasing platelet formation activity, that a pharmaceutical composition combining the two would similarly be useful in increasing platelet formation activity and would render claim 10 obvious. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). It would have been obvious to one of ordinary skill in the art at the time of the invention that the combined use of the two entities would not actively compete without evidence to the contrary and that the greater amount of each compound that was administered, the greater the effect (increased platelet

production) would be observed. These combined findings render claims 1-6 obvious.

It would have been obvious to one of ordinary skill in the art at the time of the invention that the pharmaceutically acceptable excipients taught by Sugasawa et al. would be some of the same excipients used to formulate the present invention (rendering instant claim 7 obvious). It would have been obvious to one of ordinary skill in the art at the time of the invention that as taught by Mutschler et al., multiple administration routes and dosage forms would exist depending on the site of administration. One of ordinary skill could modulate the release of the compounds depending on pharmaceutical formulation (rendering claims 8-10 obvious).

Therefore, the teachings of Sugasawa et al. in view of all Vadhan-Raj et al. and Mutschler et al. render the claimed invention obvious.

No claims allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph S. Kudla whose telephone number is (571) 270-3288. The examiner can normally be reached on 9am - 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Appendix F

Notification of Reasons for Refusal

Patent Application No. 2003-562111
Drafting Date: 2007/11/30
Japanese Patent Office Examiner: Tomoyo Ando
Patent Agent: Taku Morita
Applicable Provisions: Section 29(1), Section 29(2), Section 36

This patent application is refused due to the reasons described below. Should you have an opinion on this issue, please submit an argument within 60 days of the date of mailing of this notice.

Reasons

1. Inventions specified in the following claims of this application were publicly accessible invention prior to the patent application submission through inventions described in publications in Japan or oversea cited below or telecommunication, and therefore, fall under the Japanese Patent Law Section 29(1)iii and are not patentable.

2. Inventions specified in the following claims of this application were publicly accessible invention prior to the patent application submission through inventions described in publications in Japan or oversea cited below or telecommunication, and a person having ordinary skill in the art could easily invent them prior to the patent application, and therefore, the inventions fall under the Japanese Patent Law Section 29(2) and are not patentable.

3. This application is not meeting requirement specified in the Japanese Patent Law Section 36(6)ii with respect to its description of the claims described below.

Records (For cited literature, please see the List of Cited Literatures)

[1] Claims 1-3/Reason 2/Cited Literature 1
The cited literature 1 describes that 2-acylaminothiazole derivatives which may contain a heteroaryl group at the position 5 of thiazole can produce platelet-producing megakaryocytes (Claim 16, examples on pages 318-321, and compounds J11-J17 on page 76), and a person having ordinary skill in the art can easily perform the confirmation of the effects of -acylaminothiazole derivatives which may contain a heteroaryl group at the position 5 of thiazole described in the claims 1-3.

Also, it is not conceivable that all of the compounds in the claims 1-3 exhibit significant effects beyond the expectation of a person skilled in the art.

[2] Claim 4/Reason 2/Cited Literatures 1 and 2
Since it has been known that c-mpl ligands can produce platelet-producing megakaryocytes and increase platelet production (Cited Literature 1, page 2, [0001]-[0006]), it is easy for a person skilled in the art to perform the confirmation that the megakaryocyte-producing compounds described in the cited literature 1 are c-mpl ligands.

[3] Claim 5-9 and 14/Reasons 1 and 2/ Cited Literature 3
The cited literature 3 discloses 2-acylaminothiazole derivatives specified by formula (V) of the claims 5-9 and drug products containing these compounds (see its claims).
In addition, a person skilled in the art can readily anticipate compounds bearing substituents exemplified in the cited literature.

[4] Claim 15-17 and 14/Reason 2/ Cited Literatures 1-4
Please refer to [1]-[3].
The cited literature 4 cites that 2-acylaminothiazole derivatives can be used as thrombocytopenia-treating agents (see its claims), and a person skilled in the art can readily perform the testing of structurally extremely close compounds in the cited literatures 1 and 3 for their platelet production enhancing effects, and compounds in the cited literature 3 for their interaction with c-mpl.
Furthermore, the observed effects are not considered extraordinary.

[5] Claim 1-9, 12, 14-17/ Reason 3
It is not clear what types of substituents are covered by the description "may be substituted" found in the claim 1 and other parts.
Therefore, inventions described in the claims 1-9, 12, and 14-17 are not clear.

<Claims in which reasons for refusal are not identified>
At this point, reasons for refusal are not found in the inventions described in the claims 10, 11, and 13. A notice will be given in the event reasons for refusal are newly identified.

List of Cited Literatures.
1. WO 01/53267
2. JP-A-H11-152276
3. JP-A-H05-155871

4. WO 00/17175

Record of Prior Art Reference Search Results

- Fields searched IPC C07D, A61K
  Name of DB CAPLUS (STN), CAOLD (STN), REGISTRY (STN)
- Prior Art References

WO 02/062775
WO 02/042298
WO 02/062792
WO 01/007423
JP-A-H3-068567
JP-A-H3-173876

This Record of Prior Art Reference Search Results does not constitute the reasons for refusal.

Please contact the examiner listed below for further clarification of the contents of this Notification of Reasons for Refusal

TEL 03-3581-1101 ext3492
Patent Examination Third Division 3 Pharmaceutical Compounds Examiner Tomoyo Ando